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Pregnancy Outcome Following Maternal Use of the New Selective Serotonin Reuptake Inhibitors

A Prospective Controlled Multicenter Study

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Context.—Although a large number of women of reproductive age use new selective serotonin reuptake inhibitors (SSRIs) and half of all pregnancies are unplanned, no data exist on the safety of these agents for the human fetus.

Objective.—To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline.

Design.—A prospective, multicenter, controlled cohort study.

Setting.—Nine Teratology Information Service centers in the United States and Canada.

Patients.—All women who were counseled during pregnancy following exposure to a new SSRI and followed up by the participating centers. Controls were randomly selected from women counseled after exposure to nonteratogenic agents.

Main Outcome Measures.—Rates of major congenital malformations.

Results.—A total of 267 women exposed to an SSRI and 267 controls were studied. Exposure to SSRIs was not associated with either increased risk for major malformations (9/222 live births [4.1%] vs 9/235 live births [3.8%] in the controls, relative risk, 1.06, 95% confidence interval, 0.43-2.62) or higher rates of miscarriage, stillbirth, or prematurity. Mean (SD) birth weights among SSRI users (3439 [505] g) were similar to the controls (3445 [610] g) as were the gestational ages (39.4 [1.7] weeks vs 39.4 [1.9] weeks).

Conclusion.—The new SSRIs, fluvoxamine, paroxetine, and sertraline, do not appear to increase the teratogenic risk when used in their recommended doses.

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A DECADE after the introduction of the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, into clinical use, this class of antidepressants is being used by millions of men and women worldwide. Because more than half of all pregnancies are unplanned¹ and an estimated 8% to 20% of all women suffer from depression,² fe-

tal safety is a primary concern. During the last decade, several studies have reported on pregnancy outcome following first-trimester or whole-pregnancy exposure to fluoxetine. Although there was no evidence of major malformations or behavioral teratology,³⁻⁵ women who took fluoxetine throughout pregnancy had more perinatal complications and more minor malformations,⁴ possibly as a result of risks associated with more severe depression.

During the last few years new SSRIs have been introduced into the market.⁶ Currently, while a large number of women of reproductive age use newer SSRIs for depression and other indications (such as obsessive compulsive disorder⁷), no human data on their reproductive safety exist.

Animal teratology studies with fluvoxamine (up to 80 mg/kg per day),⁸ paroxetine (up to 43 mg/kg per day),⁹ and sertraline (up to 80 mg/kg per day)¹⁰ have

failed to show an increased risk of fetal dysmorphism or other perinatal complications. Spontaneous reports to the manufacturers are sparse and include both retrospective and prospective cases with no controls, precluding the ability to estimate fetal risk.

We report on the first prospective, controlled, cohort study of pregnancy outcome following fetal exposure to the new SSRIs.

Patients and Methods

This prospective cohort included all women who contacted 1 of 9 participating Teratology Information Service centers regarding exposure to fluvoxamine, paroxetine, and sertraline during the first trimester of pregnancy for depression. Excluded were women who, in addition to being exposed to a new SSRI, were also exposed to a known human teratogen or drugs of uncertain teratogenicity. The group exposed to SSRIs was matched to controls who were randomly selected from the total group of women counseled and followed by the Motherisk Program after exposure to agents proven to be nonteratogenic (eg, dental x-rays, acetaminophen).

During the initial interview at the time of exposure, women were asked about a variety of health-related issues including diagnosis; SSRI dose schedule and length of therapy; other drug therapy; recreational drug use; cigarette and alcohol consumption; past medical, obstetric, and genetic history; and exposure to environmental toxins. After the expected date of confinement, women were contacted and interviewed regarding the course of pregnancy, pregnancy outcome, and neonatal health. In most cases, these interviews were conducted 6 to 9 months after delivery. Reports of major malformations were corroborated with medical records.

The primary end point of interest was the rates of major malformations, de-

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Table 1.—Maternal Demographics: Exposed to Selective Serotonin Reuptake Inhibitors (SSRIs) vs Controls

Characteristic	Exposed to SSRIs, No. (n=267)	Controls, No. (n=267)	P
Gravidity			
1	57	90]. <.005
≥2	199	177	
Parity			
0	95	125]. .07
≥1	152	142	
Previous spontaneous abortion			
0	157	205]. .91
≥1	49	61	
Previous therapeutic abortion			
0	166	235]. .03
≥1	40	31	
Tobacco consumption			
Yes	74	43]. <.001
No	129	224	
Alcohol consumption			
Yes	75	98]. .94
No	130	169	
Maternal age at conception, mean (SD), y*	31.3 (4.7)	30.8 (4.9)	.29

*Maternal age was unknown for 4 SSRI cases.

defined as structural or functional anomalies that have significant medical or social consequences. The SSRI and control groups were compared on a variety of baseline characteristics and pregnancy outcome values using the unpaired *t* test (for continuous variables) or the Fisher exact test (for proportions).

Results

A total of 267 women met the study inclusion criteria (92 from Toronto, Ontario; 66 from Tampa, Fla; 46 from Philadelphia, Pa; 32 from Farmington, Conn; 11 from Salt Lake City, Utah; 7 from Burlington, Vt; 6 from London, Ontario; 4 from Chicago, Ill; and 3 from Indianapolis, Ind). A total of 147 women used sertraline, 97 used paroxetine, and 26 used fluvoxamine. One woman used both sertraline and fluoxetine, and 2 women used paroxetine and sertraline in the first trimester. Of the 267 women exposed to an SSRI, 49 used the drug throughout pregnancy. The majority of women took sertraline at a dosage of 50 mg/d (range, 25-250 mg/d), paroxetine at 30 mg/d (range, 10-60 mg/d), and fluvoxamine at 50 mg/d (range, 25-200 mg/d).

Women exposed to an SSRI were significantly less likely to be primigravid and significantly more likely to smoke cigarettes and to have had a previous therapeutic abortion than the 267 control women (Table 1). These trends were homogeneous among the 3 SSRIs (data not shown).

Pregnancy outcome did not differ between the groups, with similar rates of major malformations, spontaneous and elec-

Table 2.—Pregnancy Outcome: Exposed to Selective Serotonin Reuptake Inhibitors (SSRIs) vs Controls

Outcome	Exposed to SSRIs, No.	Controls, No.	P
Live births	222	235	.14
Spontaneous abortions	30	21	.24
Therapeutic abortions	15	9	.30
Stillbirths	0	2	.50
Major malformations	9	9	.91
Birth weight, mean (SD), g	3439 (505)	3445 (610)	.91
Gestational age, mean (SD), wk	39.4 (1.7)	39.4 (1.9)	.71

tive abortions and stillbirth, and similar mean birth weight and gestational age (Table 2). The relative risk for major malformations among SSRI-exposed neonates was 1.06 (95% confidence interval, 0.43-2.62). Table 3 presents the major malformations in the study and control groups. In addition, there were 3 cases with defined genetic syndromes (trisomy 21 and familial deafness in the SSRI group and Langer-Giedion syndrome among the controls).

Pregnancy outcome among women who took an SSRI throughout pregnancy did not differ from those who took the drug only during the first trimester. Among SSRI users, there were no differences in outcome measures between smokers and nonsmokers (data not shown).

Comment

Because half of all pregnancies are unplanned,¹ several months after the introduction of the new SSRIs into clinical use, our centers were contacted by many women who found out they had conceived while taking fluvoxamine, paroxetine, or sertraline. Moreover, other women who have benefited from these drugs wished to find out, on planning pregnancy, whether the new SSRIs are safe for their unborn fetuses.

Typically, women are excluded from premarketing clinical trials as it is perceived to be medically unethical to test drugs during human pregnancy. This results in a lack of fetal safety information on introduction of the drug into the market, and the SSRIs are not an exception.

Our study confirms animal experiments by showing that when used in the recommended doses, the new SSRIs do not appear to increase the risk of congenital malformations. Our sample size was large enough to detect a relative risk of 2.5 for major malformations with a power of 80% and an α of .05. However, the almost identical rates (9/222 vs 9/235) between the SSRI and control groups implies that thousands more cases in each group would not change this result. Our results on all measured preg-

Table 3.—Number of Major Malformations in the Selective Serotonin Reuptake Inhibitor (SSRI) and Control Groups

Malformation	No.
SSRI group	
Double urinary collecting system	2
Cardiac malformations	2
Absent corpus callosum	1
Bilateral club foot	1
Ear malformation	1
Ovarian cysts	1
Pyloric stenosis	1
Control group	
Cardiac malformations	4
Inguinal hernia	2
Undescended testicle	1
Ectopic kidney	1
Vesicourethral reflux	1

nancy outcomes are well within those reported in the general population.¹¹

Our study was not designed to address potential behavioral teratology of SSRIs. A recent study with fluoxetine failed to find differences in IQ, language, and behavior after fetal exposure to the drug.⁵ Recent findings of more minor malformations and perinatal complications among infants exposed to fluoxetine throughout pregnancy are difficult to interpret because the study did not control for depression.⁴ When controlled for depression with a group exposed to tricyclic antidepressants, infants exposed to fluoxetine in utero do not appear to have more minor malformations³ or perinatal complications (I. Nulman, written communication, October 1, 1997).

In summary, this study indicates that the new SSRIs, fluvoxamine, paroxetine, and sertraline, do not appear to increase the teratogenic risk when used in their recommended doses.

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